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09/930,125	08/14/2001	Susan Hand-Zimmermann	210121.544	9404

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/930,125	HAND-ZIMMERMANN ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *2-5 and 13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *2-5 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *January 12, 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CAR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed January 12, 2005 is acknowledged and has been entered. Claims 2-5 and 13 are pending and are currently under prosecution and an action on the RCE follows.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 2-5 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the Final Rejection mailed February 17, 2004, Section 3, pages 2-3.

Applicant argues that (a) the standard for written description is not whether explicit literal support is present but whether the skilled artisan would recognize, in view of the disclosure as originally filed, that Applicants were in possession of the invention now being claimed. The disclosure need only reasonably convey to persons skilled in the art that the inventor had possession of the subject matter in question, (b) Applicant points to the specification at page 9, lines 16-19 and page 10, lines 16-19 to show that the disclosure describes and encompasses Her-2/neu polypeptides and fragments as currently claimed and that Applicants were in possession of the claimed invention at the time the application was filed (c) in light of the disclosure the claimed polypeptides comprising the epitope of SEQ ID NO:3

and consisting of no more than amino acid residues 975-1209 of Her-2/neu are encompassed by the disclosed invention.

The arguments (a-c) have been considered but have not been found persuasive because the issue raised here is not whether Applicant had possession of the claimed invention at the time the invention was made, but rather that the newly claimed invention was not supported by the specification as originally filed. In particular, that the newly claimed limitations were not described in the specification as originally filed. A review of page 9, lines 16-19 reveals that, as stated by Applicant, the specification teaches that a polypeptide may be an entire protein or a subsequence thereof which comprise immunological epitopes. However, there is no teaching or even a contemplation that the subsequence consists of no more than amino acid residues 975-1209 of Her-2/neu. Further a review of page 10, lines 16-19 reveals that as stated by Applicant, that the specification teaches that certain polypeptides of the invention contain some or all of the Her-2/neu ICD region from about amino acid 676-1255 of SEQ ID NO:2, and more preferably comprise at least the naturally processed epitope set forth in SEQ ID NO:3. However, there is no teaching that the subsequence consists of no more than amino acid residues 975-1209 of Her-2/neu. MPEP 2163.02 is very clear in the teachings drawn to new matter. MPEP 2163 states that whenever the new matter issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. Nothing in the cited support clearly conveys the newly claimed limitations. Although the subject matter of the claim need not be described literally in order for the disclosure to satisfy the description requirement, if a claim is amended to include subject matter, limitations or terminology not present in the

application as filed, involving a departure from, addition to the application as filed, the Examiner should conclude that the subject matter is not described in that application. Since the claim was amended to include subject matter, limitations and terminology not present in the application as filed which involves both a departure from and an addition to the application as filed, Examiner properly concluded that the subject matter is not described in the application and properly rejected the newly amended claims under 35 USC 112, first paragraph. The arguments have been considered but have not been found persuasive and the rejection is maintained.

New Grounds of Rejection
Claim Rejections - 35 USC § 112

5. Claims 3-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to pharmaceutical compositions, wherein said compositions comprise a polypeptide comprises the naturally processed epitope of SEQ ID NO:3 which is a HLA-B44 restricted T-cell epitope. The specification teaches that the present invention provides methods for stimulating an immune response in a patient, preferably a T cell response, comprising administering a Her-2/neu polypeptide comprising the HLA-B44-restricted, naturally processed Her-2/neu epitope set forth in SEQ ID NO:3, wherein the patient may be afflicted with cancer and thus the cancer is treated or the patient may be considered at risk for such a disease and thus the patient is treated with the polypeptide prophylactically (p. 4, lines 21-29). Further, the specification teaches that the present invention is

directed generally to compositions and their use in therapy of cancer (p. 8, lines 25-26) and provides polypeptides capable of eliciting T cells that are immunologically reactive with one or more polypeptides described (p. 13, lines 12-19). T cells are considered to be specific for a polypeptide of the present invention if the T cells specifically proliferate, secrete cytokines or kill target cells coated with the polypeptide (p. 54, lines 18-22). T cells may be generated *in vitro* using known methods (p. 55, lines 10-15). The pharmaceutical compositions of the invention may be used for the treatment of cancer, either by treatment of active disease or by prevention (p. 73, lines 21-30). The specification exemplifies the *in vitro* development and stimulation of a T-cell cell line that specifically recognizes full length SEQ ID NO:2 and the ICD fragment of SEQ ID NO:2, amino acids 676-1255 (p. 85, lines 24-28), wherein the response is restricted to HLA-B4402 (p. 86, line 5). It was found that the T cell clone, named 17D5, recognizes SEQ ID NO:3 which corresponds to positions 1021-1030 in the Her-2/neu protein sequence of SEQ ID NO:2 (p. 87,lines 9-25). The specification exemplifies the partial protection of mice in an animal model wherein two weeks following what appears to be two immunizations with a polypeptide consisting of amino acids 676-1255 of SEQ ID NO:2, the mice were challenged with subcutaneous EL4 murine thymoma cells transfected with full length human Her-2/neu (apparently SEQ ID NO:1 which encodes SEQ ID NO:2). It was found that vaccination with the protein elicits a partially protective immune response (p. 90, lines 16-25). The nature of the immune response responsible for mediating tumor protection appears to be T-cell dependent because depletion of the T-cells results in abrogation of the tumor protective response (para bridging pages 91-92). It was found that antibodies did

not contribute to the observed protection. Given these findings, the data supports the use of ICD as a vaccine for Her-2/neu-positive tumors (p. 92, lines 8-20).

One cannot extrapolate the teaching of the specification to the enablement of the claims because implicit in the recitation of a pharmaceutical composition is the *in vivo* use thereof for treatment. Given that the only treatment mode described in the specification is treatment of cancer, implicit in the claimed pharmaceutical composition is a composition for treatment of cancer. Further, one cannot extrapolate the teaching of the specification to the enablement of the claims because the model used to exemplify the claimed invention is not commensurate in scope with the claimed invention. Protection from tumor development by vaccination of mice followed by subcutaneous injection of tumor cells transfected with SEQ ID NO:1 is not commensurate in scope with the ability to use the claimed pharmaceutical composition wherein the composition is contemplated for the treatment of human breast cancer in patients who carry a tumor load. In particular, the pharmaceutical composition is clearly drawn to the *in vivo* use of the claimed polypeptide for the treatment and prevention of cancer.

However, the specification provides no guidance on how to use the claimed compositions for the prevention of cancer in humans, as contemplated given that no guidance is provided as to how to determine which patients are candidates for prevention using the claimed compositions or how to determine when such prevention should be started.

As drawn to cancer therapy with the claimed pharmaceutical composition, Boon (Adv Can Res, 1992, 58:177-210) teaches that for active immunization in human patients we have to stimulate immune defenses of organisms that have often carried a large tumor burden. Establishment of immune tolerance may

therefore have occurred and it may prevent immunization and several lines of evidence suggest that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (p. 206, para 2). Thus it would be unpredictable that administration of the pharmaceutical composition, as a cancer vaccine, into patients that already express a heavy load of the antigen would lead to an immune response against any tumor. Further, even if T-cells could be induced as contemplated, Sherman et al, (Critical Reviews in Immunol, 1998, 18(1-2): 47-54) teach that self-tolerance may eliminate T cells that are capable of recognizing antigen epitopes with high avidity. In other words, only CTLs with low affinity are left, which would not be effective for tumor treatment *in vivo*. Smith (Clin Immunol, 1994, 41(4): 841-849), teaches that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface MHC could severely limit the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specific antigen in the necessary MHC context (p.484). In agreement, Boon, *Supra* teaches even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

Further, as drawn to the pharmaceutical compositions which comprise immunogenic fragments, Murphy et al (The Prostate, 1996, 29:371-380) specifically teach a phase I clinical trial for T-cell therapy for prostate cancer using autologous dendritic cells pulsed with HLA-specific peptides from PSMA antigen.

The reference teaches that two components are required for the production of an effective T-cell immune response. The first component is that of cancer-specific antigens and the second is the requirement of efficient presentation of cancer antigen by the host's antigen presenting cells to circulating T cells in the generation of an effective anticancer response (see pages 171-172). The treatment group participants were divided into five treatment groups. The first group received the PSM-P1 peptide, the second group received the PSM-P2 peptide, the third group received autologous DC, and groups 4 and 5 received DC pulsed with either PSM-P1 or PSM-P2 (p.373, col 2, see Treatment Groups). Data from immunological monitoring studies show an increase of T cell response in Groups 4 and 5 but no significant response in Groups 1-3. These results demonstrate the requirement to have both components in the generation of an effective immune response (p. 379, para bridging cols 1 and 2). The results clearly demonstrate that the administration of prostate peptides, in the absence of pulsing into APC, did not result in effective stimulation and/or expansion of T-cells.

Thus based on the teaching in the art and in the specification, one cannot predict that an adequate *in vivo* T cell response useful for immunotherapy could be induced by the claimed pharmaceutical composition in patients having tumor burden.

Finally, it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been

shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of *in vivo* evidence, no one skilled in the art would accept the assertion that the invention would function as claimed, that is as a pharmaceutical composition. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed and given the information in the art, no one of skill in the art would believe it more likely than not that the invention would function as claimed in the *in vivo* environment with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue

experimentation to practice the claimed invention.

6. Claims 2-5 and 13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth SEQ ID No: 2 and a portion thereof comprising SEQ ID NO:3 and therefore the written description is not commensurate in scope with the claims drawn to an immunogenic compositions comprising a polypeptide comprising the naturally processed epitope of SEQ ID NO:3 and consisting of no more than amino acid residues 975-1209 of human Her-2/neu.

It is noted that the recitation of "eliciting an immune response" is not considered a descriptive function for either the claimed compositions or for the claimed polypeptide comprising because all proteins will elicit an immune response under appropriate circumstances

The specification discloses a human Her-2/neu, SEQ ID NO:2 and a 10mer T-cell epitope identified therein, SEQ ID NO:3. The claims, as written, however, encompass polypeptides which vary substantially in length and also in polypeptide composition. The broadly claimed genus encompasses not only a polypeptide which consists of SEQ ID NO:3 and a polypeptide that consists of no more than amino acid residues 975-1209 of human Her-2/neu, but also encompasses polypeptides incorporating only portions of the claimed range of amino acid residues and incorporating only SEQ ID NO:3.

The instant disclosure of a single species of amino acid sequence and a subsequence therein does not adequately describe the scope of the claimed genus,

which encompasses a substantial variety of subgenera. Although drawn to the DNA arts, the findings in Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) are appropriate to the instant rejection. The Court found that a description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly & Co., 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Given that the specification describes only SEQ ID NO:2 and fragments thereof, it is clear that a representative number of species falling within the genus is not provided. Further, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polypeptides.

It is noted here that Bowie et al (Science, 1990, 257:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function and further teaches that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. (col 1, p. 1306). Bowie et al further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function

relationship and these regions can tolerate only conservative substitutions or no substitutions (col 2, p. 1306). Given the teachings of Bowie et al, it is clear that the effects of the addition of unlimited and undefined amino acid residues to SEQ ID NO:3, as encompassed by the claims, would be expected to result in an alteration of the three dimensional structure of the naturally processed T-cell epitope, SEQ ID NO:3 altering its functional activity. Even if the structure and function of SEQ ID NO:3 is not altered in the composition consisting essentially of SEQ ID NO:3, claim 13, the claim is not limited to an immune response to SEQ ID NO:3, but reads on an immune response to any undefined polypeptide sequence which is attached to SEQ ID NO:3

Further, given the undefined and unlimited nature of the claimed polypeptides, it is apparent that the functions of the undefined and claimed polypeptides of claims 2-5 would be both unknown and highly varied given that the claims are not limited to an immune response to any of SEQ ID NO:3, residues 975-1209 of human Her-2/neu, or even to human Her-2/neu. The claims read on an undefined immune response to an undefined polypeptide sequence.

For the reasons set forth above, there is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Furthermore, given only the disclosed sequences, given that both the structure and function of the claimed polypeptides are highly varied, given that prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to identify the polypeptides encompassed, one would reasonably conclude that the invention was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection may be obviated, for example, by amending claims 2-5 and 13 to recite a polypeptide composition comprising a polypeptide consisting of.....

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 2-5, 13 are rejected under 35 U.S.C. § 102(b) as being anticipated by US Patent No. 5,869,445.

The claims are drawn to an isolated polypeptide composition/pharmaceutical composition effective for eliciting an immune response comprising no more than amino acid residues 975-1209 but including SEQ ID NO:3/consisting essentially of SEQ ID NO:3.

It is noted that MPEP 211.03 specifically teaches that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Given the teachings set forth below, it is clear that the constructs of 5,869,445 do not alter the basic and novel characteristics of the immunogenic polypeptides claimed in claim 13. Thus, for examination purposes, the claim reads on a composition comprising a polypeptide consisting of human Her-2/neu (comprising SEQ ID NO:3) or consisting of an immunogenic portion

thereof which comprises SEQ ID NO:3 that do not materially affect the basic and novel immunological characteristics of the claimed invention.

It is further noted that Claims 2-5, 13 recite the claimed composition effective for eliciting an immune response, a pharmaceutical composition. However, these limitations are viewed as a recitation of intended use and therefore are not given weight in comparing the claim with the prior art. The claims read on the ingredient *per se*, which is a polypeptide comprising the naturally processed epitope of SEQ ID NO:3 and consisting of no more than amino acid residues 975-1209 of human Her-2/neu/consisting essentially of SEQ ID NO:3.

US Patent No. 5,869,445, as drawn to claim 13, teaches a human Her-2/neu (hHNP) comprising SEQ ID NO:2 (see SEQ ID NO:2 which is 100% identical to the instant SEQ ID NO:2) and claims a method for eliciting or enhancing an immune response to HER-2/neu protein comprising administering to a human an amount of polypeptide effective to elicit or enhance said response wherein the polypeptide has the amino acid sequence of SEQ ID NO:2 from amino acid 676 through amino acid 1255 wherein the polypeptide is in combination with a pharmaceutically acceptable carrier or diluent (see claims 1, 3 and 4). Further, as drawn to claims 2-5 and 13, the specification teaches that DC cultures were incubated for 16-18 hours with hHNP and then incubated with naïve CD4+ T lymphocytes. Proliferative response of the T cells was measured and responses of the T cells to hHNP were obtained. Given that SEQ ID NO:3 is a naturally processed T cell epitope of hHNP it would be expected that at least a subset of the incubated dendritic cells comprise the claimed amino acid sequences. Although the patent does not specifically teach that a subset of the incubated dendritic cells display the naturally processed epitope of SEQ ID NO:3 or that a subset of the

incubated dendritic cells display a polypeptide comprising SEQ ID NO:3, consisting of no more than amino acid residues 975-1209 of hHNP, the claimed polypeptides appear to be the same as the prior art polypeptides displayed on at least a subset of the cultured dendritic cells, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product used in the claimed method is different from that taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989). Finally, given that the dendritic cells were successfully used to stimulate CD4+ T lymphocytes, implicit in the process of stimulating the CD4+ T lymphocytes is the cultured dendritic cells in an immunogenic composition. All of the limitations of the claims are met.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

10. Claims 2-5 and 13 are rejected under 35 USC 102(e) as being anticipated by US 2002/0177567, of record.

It is noted that the limitations of the claims drawn to "effective for eliciting

an immune response" are viewed as an intended use of the claimed product and therefore are not given weight in comparing the claim with the prior art. Claims 2 and 13 read on the product *per se*, which is an polypeptide comprising the naturally processed epitope of SEQ ID NO:3 and consisting of no more than amino acid residues 975-1209 of human Her-2/neu, consisting essentially of SEQ ID NO:3

The claims are drawn to an isolated polypeptide composition effective for eliciting an immune response, said polypeptide comprising the naturally processed epitope of SEQ ID NO:3 and consisting of no more than amino acid residues 975-1209 of human Her-2/neu, a pharmaceutical composition comprising said range of sequences/ a composition consisting essentially of SEQ ID NO:3.

US 2002/0177567 teaches as set forth previously, in short, a polypeptide comprising a 59 amino acid fragment of human Her-2/ner, SEQ ID NO:5 which has 100% Identity to a portion of SEQ ID NO:2 within the claimed range which comprises SEQ ID NO:3, wherein said polypeptide consists essentially of SEQ ID NO:3. The reference further teaches that fusion proteins according to the invention may be present in compositions that include a pharmaceutically acceptable carrier or diluent (para 0011). The specification further teaches that the fusion proteins of the invention, based on particular portions of the protein expression product of the HER-2/neu gene, are capable of eliciting an antibody response (para 0071) and, as previously set forth, the specification points specifically to the 59 amino acid fragment wherein said fragment of human HER-2/neu shares no identity with the corresponding part of other tyrosine kinase receptors. All of the limitations of the claims are met. Finally, the reference teaches that the present invention is generally directed to HER-2/neu fusion proteins and pharmaceutical compositions comprising said HER-2/neu fusion proteins (see abstract). One would instantly

envision said pharmaceutical compositions comprising a pharmaceutically acceptable carrier and as claimed in claims 10, 12 and 14 that the pharmaceutical composition would comprise an immunostimulant, an adjuvant. All of the limitations of the claims are met.

Some of the arguments drawn to the previous rejection of the claims under 35 USC 103 are relevant to the instant rejection.

Applicant argues that the teachings of 2002/0177567, as a whole, have not been properly considered by the examiner. Although Applicants acknowledge that the cited reference teaches an isolated polypeptide consisting of no more than amino acid residues 975-1209 of human Her-2/neu, the reference teaches that the described SEQ ID NO:5 is used in a fusion with a separate and distinct polypeptide but never alone as an isolated polypeptide itself and thus the cited reference cannot render obvious Applicants claimed polypeptide when the reference explicitly requires that the described SEQ ID NO:5 be used in fusion with another polypeptide.

The argument has been considered but has not been found persuasive because Applicant is arguing limitations not recited in the claims as currently constituted. The instant claims are drawn to an isolated polypeptide **comprising** (emphasis added) the processed epitope of Her-2/neu and consisting of no more than amino acid residues 975-1209 of Her-2/neu. Given that SEQ ID NO:3 is a portion of Her-2/neu, the claim is properly interpreted as comprising a sequence of Her-2/neu consisting of no more than amino acid residues 975-1209. As defined by the MPEP 2111.03, the term comprising "is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps.

Although the phrase "consisting of " is defined by the MPEP as "excludes any element, step, or ingredient not specified in the claim. *In re Gray*, 53 F.2d 520, 11 USPQ 255 (CCPA 1931); *Ex parte Davis*, 80 USPQ 448, 450 (Bd. App. 1948) ("consisting of" defined as "closing the claim to the inclusion of materials other than those recited except for impurities ordinarily associated therewith."). The MPEP further states that when the phrase "consists of" appears in a "clause of the body of a claim, rather than immediately following the preamble, it limits only the element set forth in that clause; other elements are not excluded from the claim as a whole. *Mannesmann Demag Corp. v. Engineered Metal Products Co.*, 793 F.2d 1279, 230 USPQ 45 (Fed. Cir. 1986)." Thus the claimed invention is drawn to a polypeptide comprising no more than amino acid residues 975-1209 of human Her-2/neu, which includes SEQ ID NO:3, and the fusion polypeptide of the prior art reference reads on the instantly claimed invention.

Further, as drawn specifically to claim 13, the MPEP, 2111.03 defines the phrase "consisting essentially of" as limiting the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976) (emphasis in original). Given that the instant prior art reference clearly teaches that the fusion protein is capable of producing antibodies, it is clear that the composition is effective for eliciting an immune response and that the addition of the additional fusion protein sequences does not materially affect the basic and novel characteristics of the claimed invention. The arguments are not found persuasive and the newly imposed rejection is not overcome.

Obviousness-Type Double Patenting

9. The non-statutory double patenting rejection, whether of the obviousness type or non-obviousness type, is based on a judicially created doctrine grounded in public policy (a policy relected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 438, 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed b the assignee must fully comply with 37 CFR 3.73(b)

10. Claim 13 is rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claims 1 and 2 of US Patent No. 6,075,122.

It is noted that MPEP 211.03 specifically teaches that the transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. Given that SEQ ID NO:3 is a naturally processed T cell epitope found on human Her-2/neu, it is clear that the claim reads on the full sequence of human Her-2/neu comprising SEQ ID NO:3 as well as subsequences of human Her-2/neu comprising SEQ ID NO:3 because neither the full sequence

nor the subsequence will affect the basic and novel characteristic, that is the characteristic of being an immunogenic polypeptide which is a naturally processed T cell epitope. Thus for examination purposes, the claim reads on a composition comprising human Her-2/neu or a subsequence thereof which comprises SEQ ID NO:3.

It is further noted that Claim 13 recites the claimed composition effective for eliciting an immune response. However, this limitation is viewed as a recitation of intended use and therefore is not given weight in comparing the claim with the prior art. The claim reads on the ingredient *per se*, which is a polypeptide consisting essentially of the naturally processed epitope of SEQ ID NO:3.

Claim 13 is drawn to an isolated polypeptide composition effective for eliciting an immune response, said polypeptide consisting essentially of SEQ ID NO:3.

US Patent No. 6,075,122 claims a peptide consisting of amino acids 676-1255 of SEQ ID NO:68/ SEQ ID NO:69 (claims 1 and 2) which are 100% identical to amino acids 676-1255 of the instant SEQ ID NO:2 wherein said sequence consists essentially of SEQ ID NO:3. Further, the specification teaches that immunization of an individual with a HER-2/neu peptide (i.e., as a vaccine) can induce continued expansion in the number of T cells necessary for therapeutic attack against a tumor in which the HER-2/neu oncogene is associated. Preferred peptides for immunization are those that include all or a portion of the amino acid sequence shown in FIG. 1 beginning at about the lysine residue at amino acid position 676 and extending to about the valine residue at amino acid position 1255. US Patent No. 6,075,122 further teaches that in addition to the HER-2/neu peptide (which functions as an antigen), it may be desirable to include other components in

the vaccine, such as a vehicle for antigen delivery and immunostimulatory substances designed to enhance the protein's immunogenicity. Examples of vehicles for antigen delivery include aluminum salts, water-in-oil emulsions, biodegradable oil vehicles, oil-in-water emulsions, biodegradable microcapsules, and liposomes.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a polypeptide composition effective for eliciting an immune response, said polypeptide consisting essentially of SEQ ID NO:3, given that US Patent No. 6,075,122 expressly contemplates said immunogenic composition wherein the specification specifically teaches a vaccine comprising a polypeptide consisting of SEQ ID NO:69, amino acids 676-1255 of the instant SEQ ID NO:2, and teaches in addition to antigen, it may be desirable to include other components in said vaccine for antigen delivery as well as immunostimulatory substances designed to enhance the protein's immunogenicity. Examples of vehicles for antigen delivery include aluminum salts, water-in-oil emulsions, biodegradable oil vehicles, oil-in-water emulsions, biodegradable microcapsules, and liposomes. One would have been motivated to combine SEQ ID NO:69 with immunostimulatory substances and antigen delivery vehicles to make a polypeptide composition effective for eliciting an immune response because US Patent No. 6,075,122 specifically teaches the desirability of the combination.

7. Claims 2-5 and 13 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-5 are indefinite because claim 2 recites the phrase "no more than

amino acid residues 975-1209 of human Her-2/neu." The claims are indefinite because claim 2 provides no frame of reference and no specific human Her-2/neu is in fact claimed. Although the specification states that SEQ ID NO:1 sets forth a DNA sequence encoding the Her-2/neu protein and that SEQ ID NO:2 sets for the amino acid sequence for said Her-2/neu protein (p. 7, lines 15-18) this teaching is not limiting. In particular, because Casalini P et al (Atlas Genet Cytogenet Oncol Haematol. December 2004) specifically teaches that there are numerous alternatively spliced mRNA's of human Her-2/neu, some encoding different isoforms of human Her-2/neu and others that have not been fully characterized. The rejection may be obviated by amending the claim to recite, for example, no more than amino acid residues 975-1209 of SEQ ID NO:2.

Claims 2-5 and 13 are indefinite because claims 2 and 13 recite the phrase "effective for eliciting an immune response". Given that the broadly written claims, wherein the antigenic polypeptide is not limited to SEQ ID NO:3 or a sequence of a human Her-2/neu, reads on undefined amino acid sequences to which immune response would also be expected, the phrase is indefinite because it is not possible to determine the metes and bounds of the patent protection sought. The rejection can be obviated by amending claims 2 and 13 to recite, for example, an immune response specific for SEQ ID NO:3 or specific for a polypeptide consisting of no more than amino acid residues 975-1209 of SEQ ID NO:2 wherein said polypeptide comprises SEQ ID NO:3

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar
Primary Patent Examiner
March 31, 2005